#11

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: §
Steinke, et al. §
§
Serial No.: 07/953,680 §
§
Filed: September 29, 1992 §
§
For: METHOD AND APPARATUS FOR §
DIRECT SPECTROPHOTOMETRIC §
MEASUREMENTS IN UNALTERED §
WHOLE BLOOD §

Group Art Unit: 2505

Examiner: K. Hantis

Atty Dkt.: UTSK:142/BAH

CERTIFICATE OF MAILING
37 C.F.R. 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date below:

3/25/94 David D. Bahler
Date

DECLARATION UNDER 37 C.F.R. § 1.132

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

I, JOSEPH M. SCHMITT, a citizen of the United States, hereby declare and state:

1. I have a B.S. degree in biomedical engineering/pre-med, which was conferred upon me by Case Western Reserve University, Cleveland, Ohio in 1981, and M.S. and Ph.D. degrees in electrical engineering which were conferred upon me by Standford University, Standford, California, in 1983 and 1986, respectively. My Ph.D. thesis, published in March, 1986, was entitled "Optical Measurement of Blood Oxygen by Implantable Telemetry."

2. I have been employed from July, 1988 to present as a Senior Staff Fellow in the Biomedical Engineering and Instrumentation Program of the National Institutes of Health, Bethesda, Maryland.

3. Beginning with my graduate study at Stanford, I have been involved in the study of whole-blood oxymetry. I have authored numerous articles on this topic, and have developed and used optical methods for the measurement of oxygen concentration in whole blood. Attached to this declaration is my *Curriculum Vitae* which summarizes my education and employment, and which includes a list of my publications.

4. I have read the above-identified application, including claims 1-33, have read the Office Action mailed by the United States Patent and Trademark office on October 1, 1993, and have read the reference applied by the Examiner to reject claims 1-33, (*Anderson et al.*, "Light-Absorbing and Scattering Properties of Non-Haemolysed Blood," *Phys. Med. Bio.*, Vol. 12, 2:173-184 (1967)).

5. The purposes of the *Anderson et al.* reference as stated by *Anderson et al.* (page 174, second full paragraph) was:

> "(a) to investigate the light-scattering and light-absorbing property of non-haemolyzed blood,
>
> (b) to evaluate separately the amount of light absorbed and the amount scattered by thin layers of flowing non-haemolyzed blood by applying a theory for the multiple scattering of waves, and
>
> (c) to test the general validity of the empirical relationships between OD[optical density] and haemoglobin content (eqn. (1))."

The theory used was that of Victor Twersky. Not stated among the purposes of *Anderson et al.* was the determination of hemoglobin concentration from optical density.

6. Although *Anderson et al.* do not completely explain, it is readily apparent that *Anderson et al.* measured the OD of non-hemolyzed blood and made independent measurements of hemoglobin concentration [Hb] by some unspecified means. They then used curve-fitting techniques and employed arbitrary values for various parameters in Twersky's equation (*Anderson et al.*, Eqn. 5, page 175). The parameters in Twersky's equation that were set to arbitrary constant values include the parameters s and q_α/q (*Anderson et al.*, page 180, last paragraph).

7. In this way, *Anderson et al.* deduced the relative contributions that light scattering and true optical absorbance made to the optical attenuation of a particular sample of non-hemolyzed blood.

8. Contrary to the patent examiner's understanding of the *Anderson et al.* reference, *Anderson et al.* did not develop a practical method for deducing hemoglobin concentration from optical density. In fact, for simple mathematical reasons, it is impossible to solve Twersky's equation, used by *Anderson et al.*, for a sample of whole blood of unknown composition. The reason for this mathematical impossibility is that Twersky's equation contains too many parameters for which there is no known value in a sample of whole blood of unknown composition.

9. Specifically, Eqn. 5 of *Anderson et al.* requires specific values for the parameters K′, s and q_α/q, which together quantify: the refractive index of plasma, the refractive index of red cells, and the factor L which depends on the size and shape of red blood cells 6. Because each of these factors can vary in an unpredictable way from one blood sample to another, it is

not possible to solve Twersky's equation for hemoglobin concentration in a sample of whole blood of unknown concentration.

10. Furthermore, Twersky's equation is a theoretical description of ideal whole blood that does not accommodate causes of scattering other than red blood cells. Other factors that influence light scattering in a sample of whole blood of unknown composition include: the different plasma protein concentrations that determine the refractive index of plasma in one sample vs. another; the aggregation of red blood cells in the sample; the different hemoglobin concentrations inside the red blood cells that alter their refractive index; the size and shape of the red blood cells; chylomicrons or other light-scattering lipid particles; cell fragments; microscopic clots; light-sieving effects of sedimented red blood cells; and partial hemolysis.

11. In addition, it should be noted that in order to generate their curves, *Anderson et al.* must necessarily alter the hemoglobin concentration of the samples under study. According to *Anderson et al.* altered hemoglobin concentration is accomplished by suspending fully oxygenated non-hemolyzed red cells in isotonic saline (*Anderson et al.*, page 177, second paragraph).

12. The methods disclosed in the subject patent application enable accurate measurement of five hemoglobin species in non-hemolyzed blood. I am aware of no other methods with this capability, although there have been many previous attempts by others during the last 20 or more years. The failure of these earlier attempts can be ascribed to their inability account for the many factors underlying the blood sample-to-sample variability, which include those factors listed in paragraph 10 of this declaration.

13. In my opinion, the patent examiner has mistakenly interpreted the paper of *Anderson, et al.* as a solution to the problem of quantifying the states and concentrations of hemoglobin in whole blood. *Anderson, et al.* simply used Twersky's theory, a simplified model of light-scattering in dense suspensions, to fit observed changes in the optical density of whole blood when its total hemoglobin was altered.

14. In contrast to the present patent application, *Anderson et al.* did not consider the effects of the factors listed in paragraph 10 of this declaration that affect the optical density of blood from patient to patient or even of the blood of a single patient over time.

15. The disclosure of *Anderson, et al.* cannot be used as a basis for a practical measurement technique. In fact, it is apparent to me that none of the methods disclosed in the present patent application were contemplated by, or would have been obvious in light of, the disclosure of *Anderson, et al.*

16. The prior art references of which I am aware, including *Anderson, et al.*, do not teach to one of ordinary skill in this technology, and do not teach to me personally, how to make or use the invention claimed in the above-identified U.S. patent application. Moreover, even in view of the scope and content of the disclosure of that prior art, the invention as claimed in this application as a whole would not have been obvious at the time the invention was made to a person having ordinary skill in this technology.

17. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States

Code, and that such willful false statements may jeopardize the validity of the above-identified application, or any patent issuing therefrom.

2/25/94
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Education:

	Stanford University Stanford, CA	Ph.D., electrical engineering, March 1986
		M.S., electrical engineering, March 1983
	Case Western Reserve U. Cleveland, OH	B.S., biomedical engineering/ pre-med., May 1981; (Highest Honors)

Employment:

7/88-present Senior Staff Fellow
Lasers and Modern Optics Group
Biomedical Engineering and Instrumentation Program
National Institutes of Health, Bethesda, MD

Co-founded a laboratory dedicated to the development of non-invasive technologies for medical diagnostic applications. I have been responsible for conceiving and implementing many of the ideas that underlie our group's research and development efforts.

5/93-present Consultant -- Research and Development
Nellcor, Inc.
25495 Whitesell St.
Hayward, CA 94545

Design and recommend methods for fetal monitoring by pulse oximetry.

Consultant -- International Development

2/93 -3/93 Project HOPE
Shanghai, China

6/90-7/90 World Health Organization
Truk and Kosrae, Micronesia

4/86-5/86 Project HOPE
Kingston, Jamaica

Trained biomedical engineering technicians and engineers in developing countries in cooperation with national health ministries.

5/86- 5/88 Biomed. Engin. Coordinator
Project HOPE, Zhejiang Medical University
Hangzhou, People's Republic of China

Developed biomedical engineering and technician training programs in medical schools; helped establish hospital equipment-maintenance departments. My efforts were part of a long-term plan to modernize the technological capabilities of hospitals in mainland China.

8/81-4/86 Graduate Research Assistant
Center for Integrated
Electronics in Medicine,
Stanford, CA

Designed and fabricated implantable integrated circuits; developed new methods for whole-blood oximetry on which sensors now used in heart-lung bypass machines are based.

6/81-8/81 Biomedical Engineer
Case Western Reserve University
Cleveland, OH

6/80-9/80 Junior Engineer
Food & Drug Administration
Bureau of Radiological Health
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6/79-8/79 Research Assistant
Institute for Sensory Research
Syracuse, NY

Honors: NIH Special Act Award (1991), Honorary Certificate of Merit and Visiting Professorship (Zhejiang Medical University, P.R. China, 1988-), Mark Bernstein Award (Biomedical Engineering, 1981), Reinberger Memorial Scholarship (1978-1981), Bausch & Lomb Mathematics Award (1977), High school valedictorian.

Other Skills/ Activities: Fluent in Mandarin Chinese and conversant in Spanish; active in international technological development programs.

PUBLICATIONS (in reverse chronological order)

Papers

A. Knüttel, J.M. Schmitt, M. Shay, and J.R. Knutson, "Stationary Low-Coherence Light Imaging and Spectroscopy Using a CCD Camera," *Proc. SPIE* , submitted for publication (12/93).

J.M. Schmitt, A. Knüttel, and M. Yadlowsky, "Interferometric Versus Confocal Techniques for Imaging Microstructures in Turbid Biological Media ," *Proc. SPIE* , submitted for publication (12/93).

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A.H. Gandjbakhche, J.M. Schmitt, R. Bonner, and R. Nossal, "Random Walk Theory Applied to Noninvasive In Vivo Optical Measurements of Human Tissue," *Proc. 14th Annual Intern. Conf. IEEE EMBS*, Paris , France, Oct. 29-Nov. 1, 1992, pp. 332-333.

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JM. Schmitt, G.X. Zhou, E.C. Walker, and R.T. Wall, "Multi-layer Model of Photon Diffusion in Skin," *J. Opt. Soc. Am. A* , 7 (11), 1990, pp. 2141-2153.

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J.M. Schmitt, D. Harame, and L. Bousse, "Implantable Chemical Sensors for Blood Gas Analysis," in Methods of Animal Experimentation (Vol. VII) (W.I. Gay and J.E. Heavner, eds.) , Academic Press, New York, 1986, pp. 67-71.

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J.M. Schmitt, J.D. Meindl, and F.G. Mihm, "An Integrated-Circuit-Based Optical Sensor for In Vivo Measurement of Oxygen Saturation, " *IEEE Trans. Biomed. Eng.*, 33, 1986, pp. 98-107.

L. Bowman, J.M. Schmitt, and J.D. Meindl, "Electrical Contacts to Implantable Integrated Sensors by CO_2 Laser-Drilled Vias in Glass, " in Micromachining and Micropackaging of Transducers (C.D. Fung, P.W. Cheung, W.H. Ko, and D.G. Fleming, eds.), Elsevier Press, New York, 1985, pp. 79-84.

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J.M. Schmitt, M. Baer, M.F. Anderson, F.G. Mihm, and J.D. Meindl, "Inhibition of Thrombus Formation on Intravascular Sensors by Electrical Polarization, " *J. Biomed. Mater. Res.*, 18, 1984, pp. 797-807.

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Patents

J.M. Schmitt, E.C. Walker, and R.L. Webber, "Pulse Oximeter for Diagnosis of Dental Pulp Pathology" (U.S. Pat.07/350,908).

(Pending) J.M. Schmitt, "Optical Method for Monitoring Arterial Blood Hematocrit" (U.S. Pat. Appl. 07/822,018).

(Pending) J.R. Knutson, A. Knüttel, and J.M. Schmitt, "Differential Diffusive Waves: Optical Frequency Modulation-Diffusive Wave Detection Methods for Localization and Spectroscopy of Objects inside Turbid Media." NIH patent application in process.